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Rapid Detection of Methicillin Resistance in Coagulase-Negative Staphylococci with the VITEK 2 System

Matthias A. Horstkotte,* Johannes K.-M. Knobloch, Holger Rohde, Sabine Dobinsky, and Dietrich Mack

Institut für Medizinische Mikrobiologie und Immunologie, Universitätsklinikum Hamburg-Eppendorf, D-20246 Hamburg, Germany

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The aim of the present study was to evaluate the accuracy of the new VITEK 2 system (bioMérieux, Marcy l' Etoile, France) for the detection of methicillin resistance in coagulase-negative staphylococci (CoNS) by using AST-P515 and AST-P523 test cards. Analyses of the VITEK 2 oxacillin MIC determination evaluated according to the actual breakpoint (≥0.5 μg/ml) of the National Committee for Clinical Laboratory Standards resulted in a high sensitivity of 99.2% but a moderate specificity of 80%. The newly included oxacillin resistance (OR) test of the VITEK 2 system displayed a high sensitivity and a high specificity of 97.5 and 98.7%, respectively. Concordance between the results of the *mecA* PCR and the VITEK 2 oxacillin MIC was observed for almost all *Staphylococcus epidermidis* strains, but the reduced specificity was attributable to higher oxacillin MICs for *mecA*-negative non-*S. epidermidis* strains, especially *S. saprophyticus*, *S. lugdunensis*, and *S. cohnii*. Evaluation of alternative oxacillin MIC breakpoints of 1, 2, or 4 μg/ml resulted in improved degrees of specificity of 84, 90.7, and 97.3%, respectively. Only minor changes occurred in the corresponding sensitivity values, which were 98.4, 97.5, and 97.5%, respectively. Methicillin resistance in CoNS was detected after 7 and 8 h in 91.1 and 93.5% of the *mecA*-positive strains, respectively, by the VITEK 2 OR test and in 86.3 and 89.5% of the *mecA*-positive strains, respectively, by VITEK 2 oxacillin MIC determination. After 7 and 8 h the VITEK 2 OR test classified 59.2 and 78.9% of the *mecA*-negative strains, respectively, as susceptible to oxacillin, whereas comparable values were obtained 2 h later by VITEK 2 oxacillin MIC determination. The results of our study encourage the use of the VITEK 2 system, which proved to be a highly reliable and rapid phenotypic method for the detection of methicillin resistance in CoNS.

Coagulase-negative staphylococci (CoNS) rank among the five most frequent causative organisms of nosocomial infections, which are regularly associated with biomedical implants (21, 26, 35, 42, 44). Antibiotic therapy of infections caused by CoNS is increasingly problematic due to frequent multiple-antibiotic resistance (2). Most importantly, the majority of clinical CoNS harbor the *mecA* gene encoding an additional penicillin binding protein (PBP) 2a (PBP 2a) (4). Phenotypic detection of methicillin resistance in CoNS is difficult due to the heterogeneous expression of *mecA* (6, 30, 41, 47). Detection of *mecA* by PCR is very sensitive and is considered the "gold standard," but it is not feasible for the busy clinical microbiology laboratory. Detection of PBP 2a as a marker for methicillin resistance in CoNS is also rapid and reliable and has therefore been recommended as an alternative for *mecA* PCR by the National Committee for Clinical Laboratory Standards (NCCLS) (1, 13, 14, 25, 32, 43, 48).

The VITEK 2 system (bioMérieux, Marcy l'Etoile, France) is a fully automated system for rapid identification and antimicrobial susceptibility testing and is reliable for many rapidly growing bacteria (5, 8–10, 17, 19, 20, 22–24, 33, 37, 38, 45) and yeasts (12). In the earlier generation of the system, the Vitek system, detection of methicillin resistance was solely based on oxacillin MIC determination. To enhance the sensitivity and the specificity of the system, an oxacillin resistance (OR) test was introduced into the new VITEK 2 system as a second assay. The composition of the VITEK 2 OR test is comparable to that of the oxacillin agar screen. Recently, detection of methicillin resistance in *Staphylococcus aureus* with the VITEK 2 system was investigated (22, 24, 36), but detection of methicillin resistance in clinical CoNS isolates has not been studied in detail. In the present study detection of *mecA* by PCR was compared to the results of the OR test and oxacillin MIC determination with the VITEK 2 system for 200 isolates of CoNS. The time until detection of methicillin resistance was analyzed for both tests in parallel.

(Part of this work will appear in the doctoral thesis of M.A.H., Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.)

MATERIALS AND METHODS

Bacterial isolates. The CoNS strains (n = 200) belong to a collection of clinical isolates which were consecutively collected at the University Hospital Hamburg-Eppendorf in 1997 and 1998 and include 13 different species (140 *S. epidermidis*, 16 *S. haemolyticus*, 10 *S. hominis*, 9 *S. saprophyticus*, 6 *S. capitis*, 4 *S. lugdunensis*, 4 *S. warneri*, 4 *S. xylosus*, 2 *S. schleiferi*, 2 *S. cohnii*, 1 *S. chromogenes*, 1 *S. simulans*, and 1 *S. kloosii* isolates), as described previously (13, 28). *S. aureus* ATCC 29213 (*mecA* negative) and *S. aureus* ATCC 43300 (*mecA* positive) were used for quality control. The strains were kept at −80°C in microbank tubes (Pro Lab Diagnostics, Richmond Hill, Ontario, Canada) and were subcultured twice onto Columbia agar (Difco, Becton Dickinson, Sparks, Md.) plates containing 5% sheep blood in ambient air at 37°C before testing.

Antimicrobial susceptibility testing with the VITEK 2 system. The phenotypes of the strains were determined by detection of methicillin resistance by the

* Corresponding author. Mailing address: Institut für Medizinische Mikrobiologie und Immunologie, Universitätsklinikum Hamburg-Eppendorf, Martinistrasse 52 D-20246, Hamburg, Germany. Phone: 49 40/42803-3147. Fax: 49 40/42803-4881. E-mail: horstko@uke.uni-hamburg.de.

TABLE 1. Comparison of the oxacillin MIC determination and the OR test of the VITEK 2 system with the results of the *mecA* PCR

Parameter and strain	No. of strains
Concordant results between *mecA* PCR and both MIC and OR test	179
mecA-positive strains	119
mecA-negative strains	60
Indeterminate results (discrepancies between MIC and OR test) for:	16
mecA-negative strains	
S. saprophyticus group	9
S. lugdunensis	4
S. epidermidis	1
mecA-positive strains	
S. epidermidis	1
S. hominis	1
False-positive results (*mecA*-negative strain, but both MIC and OR test indicated resistance)	1
False-negative results (*mecA*-positive strain, but both MIC and OR test indicated susceptibility	1
Insufficient growth	3

oxacillin resistance (OR) test (categories of susceptible or resistant) and oxacillin MIC determination. Both tests are included in the AST-P515 antimicrobial susceptibility test cards and in the newer AST-P523 antimicrobial susceptibility test cards. The AST-P523 cards differ from the AST-P515 cards only in their lower oxacillin MIC range (≤0.25 to ≥4 μg/ml versus ≤0.5 to ≥8 μg/ml) and not in the composition of the tests examined. The instructions of the manufacturer for antibiotic susceptibility testing with the VITEK 2 system were essentially followed. Reading of test cards was performed every 15 min by the VITEK 2 system, and the results for the VITEK 2 OR test and the VITEK 2 oxacillin MIC determination were recorded after every reading for up to 10 h for each isolate. Initially, all CoNS isolates were tested with AST-P515 cards. CoNS strains for which the VITEK 2 oxacillin MIC was ≤0.5 μg/ml were additionally tested with the AST-P523 card, allowing determination of lower oxacillin MICs. CoNS isolates with discrepancies between the results of the PCR for *mecA* and the VITEK 2 tests were reexamined. If an initial oxacillin MIC of ≤0.5 or 1 μg/ml was noted, retesting was performed with AST-P523 cards, whereas AST-P515 cards were used for strains for which the initial oxacillin MIC was ≥2 μg/ml. On retesting the same procedure was used as described above, and neither method was voluntarily changed.

PCR for *mecA*. PCRs were performed essentially as described previously (13, 27).

RESULTS

MecA was detected in 124 of 200 (62%) strains comprising 99 of 140 (70.7%) *mecA*-positive *S. epidermidis* strains and 25 of 60 (41.7%) *mecA*-positive non-*S. epidermidis* strains. The VITEK 2 oxacillin MIC was ≥8 μg/ml for 119 of 124 *mecA*-positive strains (Table 1). Lower VITEK 2 oxacillin MICs ranging from ≤0.25 to 2 μg/ml were found for three *mecA*-positive strains (one *S. epidermidis* strain, one *S. hominis* strain, and one *S. haemolyticus* strain (Tables 1 and 2). With the AST-P515 cards, for 63 of 76 *mecA*-negative strains the oxacillin MIC was ≤0.5 μg/ml (Table 1). For 12 *mecA*-negative strains, the VITEK 2 oxacillin MICs ranged from 1 to ≥8 μg/ml (Table 2). The 63 strains for which the initial VITEK 2 oxacillin MIC was ≤0.5 μg/ml with the AST-P515 cards were additionally tested with AST-P523 cards. An oxacillin MIC of ≤0.25 μg/ml was detected for 60 strains, but for 3 *mecA*-negative strains (1 *S. saprophyticus* strain and 2 *S. lugdunensis* strains) the oxacillin MIC was 0.5 μg/ml (Tables 1 and 2).

The VITEK 2 OR test with the AST-P515 card detected 119 of 124 *mecA*-positive strains (Table 1) but failed to indicate methicillin resistance in the 3 *mecA*-positive strains (1 *S. epidermidis* strain, 1 *S. hominis* strain, and 1 *S. haemolyticus* strain), for which VITEK 2 oxacillin MICs were ≤0.25 to 2 μg/ml (Tables 1 and 2). All *mecA*-negative strains, except 1 *S. kloosii* strain for which the VITEK 2 oxacillin MIC was ≥8 μg/ml, were correctly classified as susceptible by the VITEK 2 OR test (Tables 1 and 2).

Discrepancies between the results of the VITEK 2 OR test and the VITEK 2 oxacillin MIC determination were observed for 14 *mecA*-negative strains (6 *S. saprophyticus*, 4 *S. lugdunensis*, 2 *S. cohnii*, 1 *S. xylosus*, and 1 *S. epidermidis* strains), with VITEK 2 oxacillin MICs ranging from 0.5 to 4 μg/ml but with susceptibility indicated by the VITEK 2 OR test (Tables 1 and 2). The results for these 14 strains were categorized as indeterminate (Tables 1 and 2). Additionally, the above-mentioned *mecA*-positive *S. epidermidis* (n = 1) and *mecA*-positive *S. hominis* (n = 1) strains for which the VITEK 2 oxacillin MICs were 1 and 0.5 μg/ml, respectively, but which were susceptible by the VITEK 2 OR test were categorized as indeterminate (Tables 1 and 2). Retesting of the 16 strains categorized as indeterminate confirmed the initial VITEK 2 OR test result for all strains and the VITEK 2 oxacillin MIC did not vary significantly (Table 2).

Insufficient growth in the AST-P515 cards was observed for three strains including one *mecA*-negative *S. epidermidis* strain and two *mecA*-positive *S. saprophyticus* strains. On retesting of these strains with AST-P515 cards, one *mecA*-positive *S. sap-*

TABLE 2. Discrepant and indeterminate results of VITEK 2 tests compared to the results of the *mecA* PCR

Identification	*mecA* PCR result[a]	Oxacillin MIC (μg/ml)		Susceptibility by oxacillin resistance test[b]	
		Initial test	Retest	Initial test	Retest
S. kloosii	−	≥8	≥8	R	R
S. saprophyticus	−	4	4	S	S
S. saprophyticus	−	2	2	S	S
S. saprophyticus	−	2	1	S	S
S. saprophyticus	−	1	0.5	S	S
S. saprophyticus	−	1	2	S	S
S. saprophyticus	−	≤0.5	0.5	S	S
S. cohnii	−	2	2	S	S
S. cohnii	−	2	2	S	S
S. xylosus	−	1	0.5	S	S
S. lugdunensis	−	1	1	S	S
S. lugdunensis	−	1	0.5	S	S
S. lugdunensis	−	≤0.5	0.5	S	S
S. lugdunensis	−	≤0.5	0.5	S	S
S. epidermidis	−	2	2	S	S
S. epidermidis	+	1	2	S	S
S. hominis	+	≤0.5	0.5	S	S
S. haemolyticus	+	≤0.5	≤0.25	S	S
S. saprophyticus	+	No growth	≥8	No growth	R
S. saprophyticus	+	No growth	No growth	No growth	No growth
S. epidermidis	−	No growth	≤0.5	No growth	S

[a] +, positive; −, negative.
[b] S, susceptible; R, resistant.

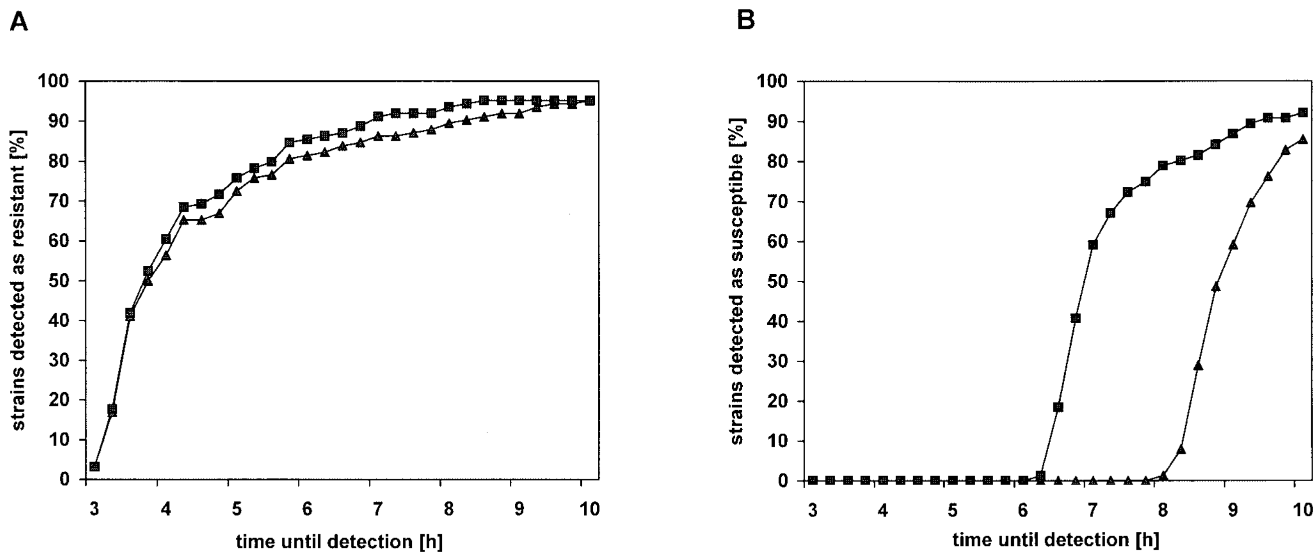

FIG. 1. Time course of results of VITEK 2 oxacillin MIC determination (▲) and VITEK 2 oxacillin resistance test (■) for *mecA*-positive CoNS strains (A) and *mecA*-negative CoNS strains (B).

rophyticus strain again did not grow, whereas susceptibility to oxacillin was correctly determined for the other *mecA*-positive *S. saprophyticus* strain and the *mecA*-negative *S. epidermidis* strain (Tables 1 and 2). Neither *S. saprophyticus* strain grew with AST-P523 cards (Table 2).

Among the *mecA*-positive strains, resistance to oxacillin was detected after 7, 8, and 9 h by the VITEK 2 OR test in 91.1, 93.5, and 95.2% of the strains, respectively (Fig. 1A), and by VITEK 2 oxacillin MIC determination in 86.3, 89.5, and 91.9% of the strains, respectively (Fig. 1B). However, among the *mecA*-negative strains, susceptibility to oxacillin was detected after 7, 8, and 9 h by the VITEK 2 OR test in 59.2, 78.9, and 86.8% of the strains, respectively (Fig. 1A), and by VITEK 2 oxacillin MIC determination in 0, 1.3, and 59.2% of the strains, respectively (Fig. 1B).

DISCUSSION

In the Vitek system, detection of methicillin resistance was solely based on oxacillin MIC determination. Three recent studies reported high sensitivities (range, 95.7 to 100%) but only a moderate degree of specificity (range, 61 to 85.5%) for the Vitek system with CoNS (25, 29, 46).

To improve the rate of detection of methicillin resistance in staphylococci, the OR test was implemented in the new VITEK 2 system. Recently, VITEK 2 oxacillin MIC determination performed with excellent results for the sensitive and specific detection of methicillin-resistant *S. aureus* (36). So far, analyses of methicillin resistance in CoNS have been performed with only a small number of selected *mecA*-positive *S. epidermidis*, *S. hominis*, and *S. warneri* strains, with overall agreement with the PCR results (22, 24). When our study was evaluated according to the actual NCCLS oxacillin breakpoint (18, 32) of $\geq$0.5 μg/ml, VITEK 2 oxacillin MIC determination correctly classified 119 of 124 *mecA*-positive CoNS strains as resistant and 60 of 76 *mecA*-negative strains as susceptible, which resulted in a high sensitivity of 99.2% but a moderate specificity of 80%.

When the older NCCLS oxacillin breakpoint of $\geq$4 μg/ml is used in the evaluation, VITEK 2 oxacillin MIC determination again correctly classified 119 of 124 *mecA*-positive strains as resistant but 73 of 76 *mecA*-negative strains as susceptible, resulting in an excellent sensitivity of 97.5% and a specificity of 97.3%. Calculations based on oxacillin MIC breakpoints of 1 and 2 μg/ml yielded sensitivities of 98.4 and 97.5%, respectively, and specificities of 84 and 90.7%, respectively.

Detection of methicillin resistance in CoNS solely on the basis of the results of the VITEK 2 OR test was superior to VITEK 2 oxacillin MIC determination, with a sensitivity of 97.5% and a specificity of 98.7%. Remarkably, 14 of the 16 strains with susceptibility by the VITEK 2 OR test but for which the VITEK 2 oxacillin MIC was above the actual NCCLS breakpoint were non-*S. epidermidis* strains, consisting of 6 *S. saprophyticus*, 4 *S. lugdunensis*, 2 *S. cohnii*, 1 *S. xylosus*, and 1 *S. hominis* strains but only 2 *S. epidermidis* strains. Another characteristic feature of strains with indeterminate results is the predominance of novobiocin-resistant species for 9 of 16 strains. Only 2 strains (1 *S. epidermidis* strain and the 1 *S. hominis* strain) classified as indeterminate were in fact *mecA* positive, but 14 of 16 strains were *mecA* negative (Table 1 and 2).

Only one *mecA*-negative *S. kloosii* strain displayed a false-positive result, with a VITEK 2 oxacillin MIC of $\geq$8 μg/ml and resistance by the VITEK 2 OR test (Tables 1 and 2). The molecular basis of decreased susceptibility to oxacillin in *mecA*-negative CoNS warrants further investigations, but alterations in PBPs other than PBP 2a have been documented in *S. haemolyticus* and *S. saprophyticus* (40) and were suggested as one possible explanation (41). A false-negative result was observed for a *mecA*-positive *S. haemolyticus* strain for which the VITEK 2 oxacillin MIC was $\leq$0.5 μg/ml (oxacillin MIC on retesting, $\leq$0.25 μg/ml) and which was also reported to be susceptible by the VITEK 2 OR test (Table 2). The results of our study are comparable to those of recent studies in which an excellent specificity of the new breakpoint was found when it was applied to *S. epidermidis*, *S. hominis*, and *S. haemolyticus*, but the new breakpoint was less accurate when it was applied to *S. saprophyticus*, *S. cohnii*, *S. warneri*, *S. lugdunensis*, and *S. xylosus* (11, 16).

In the Vitek system, false-positive oxacillin MIC results have been observed predominantly for *mecA*-negative *S. saprophyticus* or *S. lugdunensis* strains (15, 25, 29, 46) for which oxacillin MICs are 0.5 or 1 μg/ml. Divergent results were also mentioned for *S. cohnii*, *S. sciuri*, and *S. capitis* strains (29). To enhance the specificity of the Vitek system, exclusion of *S. saprophyticus* and *S. lugdunensis* strains has been proposed (25). This proposal correlates well with the results obtained for a collection of 83 *mecA*-negative *S. saprophyticus* strains, with the oxacillin MIC for the majority of strains being 0.5 μg/ml (34). In that study, the oxacillin MIC results obtained with the Vitek system and by the broth microdilution and agar dilution methods were in good agreement. However, on the basis of the actual NCCLS breakpoint (≥0.5 μg/ml), oxacillin MIC determination with the Vitek system and by broth microdilution and agar dilution would have classified as resistant 81 of 83, 76 of 83, and 81 of 83 *mecA*-negative strains, respectively (34).

In the VITEK 2 system, the OR test leads to the specific detection of methicillin resistance; however, indeterminate results occur with the OR test, indicating sensitivity, and VITEK 2 oxacillin MIC determination, indicating resistance. If indeterminate results occur, we recommend that the results of the VITEK 2 OR test be followed. An alternative strategy would be to deduce susceptibility to oxacillin from the species identification or at least resistance to novobiocin because we observed the most indeterminate results for *mecA*-negative strains belonging to the *S. saprophyticus* group and *S. lugdunensis* (Tables 1 and 2). More isolates of the respective species must be analyzed to reach generalized conclusions, but recently, the NCCLS has also emphasized that the current interpretative criteria for the oxacillin MIC could be misleading, especially for *S. saprophyticus* and *S. lugdunensis* strains (32).

The VITEK 2 system rapidly reported the resistance results obtained by oxacillin MIC determination and the OR test: after 8 h for about 80% of the strains (Fig. 1A and B). Compared to conventional phenotypic methods, which would take up to 48 h, this substantial acceleration of the diagnostic capability with the VITEK 2 system may have a potential impact on the optimal antibiotic management of CoNS infections. Rapid antimicrobial susceptibility testing (RAST) was reported to have an important clinical impact due to decreased rates of mortality (7). Additionally, financial benefits are attributable to reduced laboratory pharmacy and other general costs, which were significantly lower for the RAST groups (3, 7).

Concerning CoNS infections, rapid and reliable detection of methicillin resistance in CoNS is highly desirable to reduce the overuse of glycopeptides for the treatment of CoNS infections. Widespread use of glycopeptides risks increasing the numbers of infections caused by vancomycin-resistant enterococci and causing the emergence of glycopeptide resistance in *S. aureus* (31, 39). In the present study the combination of the VITEK 2 OR test and VITEK 2 oxacillin MIC determination proved to be a highly sensitive, specific, and rapid procedure at least equivalent to other phenotypic techniques for the detection of methicillin resistance in CoNS, like the oxacillin spread plate technique, the method with oxacillin disk on NaCl-supplemented Mueller-Hinton agar, or the broth microdilution method. The results of our study encourage the use of the VITEK 2 system for the detection of methicillin resistance in CoNS.

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